Notes

(This page is not for submission)
Required items:

- case for support (up to eight pages)
- justification of resources (two pages)
- data management plan (DMP) (up to three pages, data management plan template) if you opt not to use the template for your plan, the topics listed in the template must be addressed in the DMP document you do provide
- diagrammatic workplan (one page)
- management structure (one page)
- narrative CV (up to two pages per staff member)
- community letters of support or demand (up to 10)
- proposal cover letter.

Contents

1 Case for support

Instructions and guidance: https://www.ukri.org/wp-content/uploads/2021/09/BBSRC-150921-FundingOpp-Bioinfor
pdf

Assessment criteria.

https://www.ukri.org/wp-content/uploads/2021/09/BBSRC-150921-FundingOpp-BioinformaticsBiologicalRe
pdf

Scientific quality and strategic relevance of the resource.

Including:

- *the extent to which the resource meets the highest international standards in resource provision in its field*
- *how well the resource is demonstrated to be unique or complementary to other similar existing resources*
- *the extent to which the resource addresses the research and policy priority areas of BBSRC.*

Cost effectiveness, particularly considerations for long-term sustainability beyond BBSRC funding.

The extent to which:

- *the resource delivers value for money relative to the anticipated scientific gains it will provide*
- *long term sustainability options have been considered, addressed, and planned where appropriate, particularly for existing resources.*

Potential for economic and social impact beyond the academic community.

Including:

- *the extent to which the outputs from the resource will contribute to knowledge and potential for economic return or social impact*
- *how well the proposal has outlined methods of engagement and measures of success in developing milestones and timelines of associated activities.*

Fit to the scope.

How well the proposal addresses the scope of the opportunity.

Assessment criteria adapted to new or existing resources

To allow for a more nuanced assessment between new and existing resources, the use of the following assessment criteria will be adapted accordingly.

For new resources, these criteria will assess the 'plans, potential, and promise' of the resources.

Quality of the overall arrangements for resource management, advisory functions, as well as user access and engagement

Including:

- *the extent to which the proposal has evidenced or planned interaction with relevant users and the broader research community to ensure the aims of the resource are realised and there is sufficient uptake and continued development*
- *the extent to which adequate user access arrangements have been discussed and considered*
- *the set-up of project management and advisory structures of the resource to ensure longevity in delivering the resource to a broad user base.*

Need or demand, and potential benefit to the UK academic research community

The extent to which:

- *the community has demonstrated demand for the proposed resource, relative to the total community size (in particular, proposals for new resources should have consulted their prospective community prior to application)*
- *the proposed resource will deliver and benefit the wider BBSRC community indicating how the proposed resource will help to deliver high-quality research.*

Section headings taken from guide. We can omit some if clearly not necessary, but should do so with caution.

1.1 Background to the Resource

Introduction of the proposed resource, including its academic and wider economic and societal context.

Overview of past and current resource(s) in the subject area in both the UK and abroad, including any alternative community resources currently available. You should indicate the community size of the intended resource and how this relates to the field in which it operates.

Experimental control and neural data analysis are currently highly disassociated. Most neuroscientists collect their data and only afterward analyze it. This split has had dramatic consequences for the progress of neuroscience. First, most experimental control methods currently do not use advanced data analysis methods to enhance their functionality. Second, the vast majority of neural data analysis methods are offline and do not provide key functionality needed for online experimental control. Using advanced data analysis methods in experimental control will improve the sophistication of experiments that are currently possible, and generate new demands for neural data analysis methods that will generate advances in the field.

A central goal of the software development proposed here is to address this problem, by providing Bonsai (an experimental control software ecosystem; Figure 1.1 and Section 1.1.1) with state-of-the-art online (and offline) data analysis methods (Figure 2 and Section **??**). It is unfortunate that neuroscientists currently do not have software that allows them to easily compare the performance of different data analysis methods for the characterization of their datasets. The second central goal of this proposal is to address this limitation by adding to Bonsai a generic mechanism for comparing the performance of different methods for the analysis of specific datasets (Section 1.2.6).

Currently Bonsai has its own package manager, and its community of users have already extended Bonsai's functionality with several contributed packages (e.g., . . . Goncalo please reference the best contributed packages developed by the Bonsai community). However, these packages need to be written in C#, while most current neuroscience data analysis methods are written in Python, R or Matlab. We propose to add to Bonsai capabilities to communicate with software written in these languages (Section 1.2.7). These capabilities will allow a large number of neuroscience data analysis methods to be easily integrated into the Bonsai ecosystem and will provide Bonsai users a large repertoire of advance machine learning methods for their behavioral and neural data analysis.

Bonsai is an excellent tool for reproducible data acquisition and experimental control. An experiment implemented in Bonsai can be replicated in a new laboratory by just sharing a Bonsai configuration file. With the addition of the proposed machine learning functionality Bonsai will extend this reproducibility to the domain of data analysis (Section 1.2.8).

1.1.1 Bonsai

Bonsai (Lopes et al., 2015; Lopes and Monteiro, 2021) is a free and open-source visual programming language that emphasizes performance, flexibility, and ease-of-use, allowing scientists with no previous programming experience to quickly develop their own high-performance data acquisition and experimental control systems (Figure 1c). Bonsai combines a high-level event algebra for data streams with an integrated development environment (IDE) and a strong library of plugins supporting multiple hardware and software packages used by the biomedical research community (Figures 1a, 1b).

Bonsai has a large user base in the systems neuroscience community. Quantifications of this user base are provided in Figures 1d-1f. In the last year alone, we estimate more than 1,000 new users have started to incorporate Bonsai into their experimental protocols across the world. The surprising rate of adoption of Bonsai in non-programmer experimental labs highlights the need for accessible programming tools that enable state-of-the-art technology but also allow researchers to stay in control and change their experimental paradigms. Many open-source software tools are either inaccessible to non-programmers, or too constrained to be of general use outside their narrow domain of application. Bonsai has been successful because it has straddled this gap to some extent.

The language has also helped to potentiate the growing wave of foundational open hardware initiatives, such as the OpenEphys (Siegle et al., 2017) and UCLA Miniscope (Cai et al., 2016), making it possible to quickly combine and integrate these tools into new experiments (Buccino et al., 2018). Bonsai has been adopted in large neuroscience undertakings like the International Brain Laboratory[1] and the Allen Institute for Brain Science[2]. More recently, Bonsai has started to expand outside the domain of neuroscience into biomedical research and biotechnology tool development, and even outside academia into public outreach and education programs.

1.2 Details of Resource

The case for support should outline the full details of the resource and associated work packages presented in the proposal.

[1] https://www.internationalbrainlab.com/
[2] https://alleninstitute.org/what-we-do/brain-science/

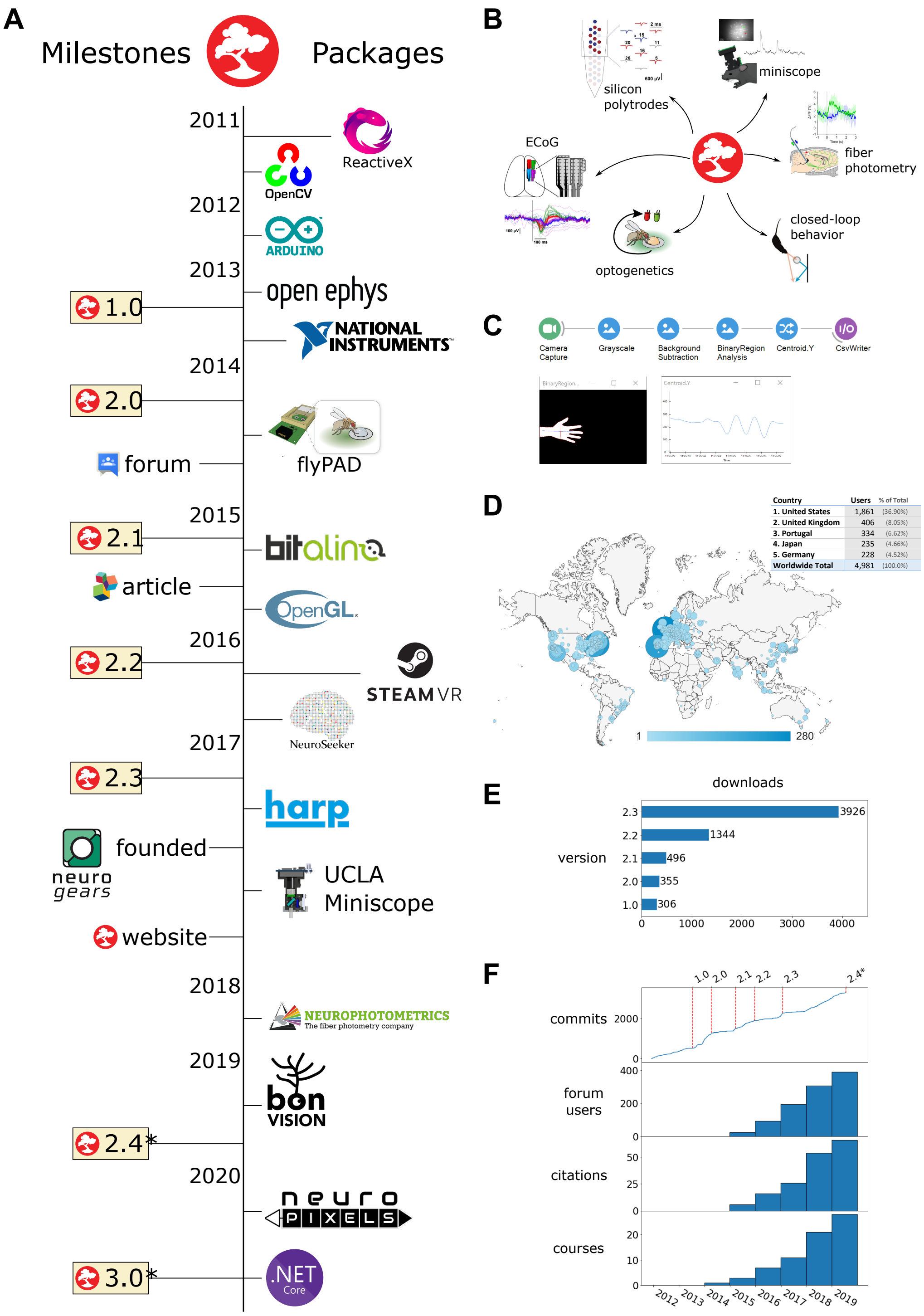

Figure 1: Bonsai development timeline and community adoption. **(A)** Timeline of milestones and landmark package releases. **(B)** Example neuroscience experiments developed in Bonsai over the years. For detailed information see references [9], [10], [11], [12], [13], [14]. **(C)** Example Bonsai workflow for tracking the position of objects in a video. **(D)** Worldwide distribution of visitors to the bonsai-rx.org website from January 2018 to July 2019. Inset table shows the top 5 countries by number of visitors. **(E)** Number of downloads for each Bonsai version. **(F)** Cumulative number of registered forum users, citations of the main publication, and number of training events, by year (bottom panels), versus release and development cycle (top panel), measured in commits to main repository. Release numbers marked with an asterisk are ongoing development.

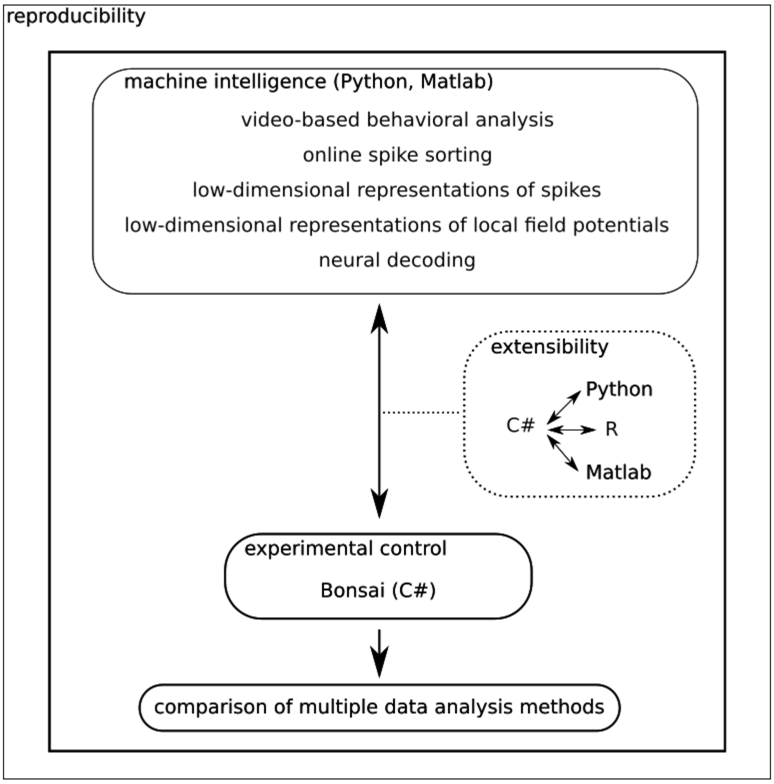

Figure 2: Proposed extensions to Bonsai

- *Indication whether the project proposed to develop a new resource or is in support of an existing one.*

Existing if general Bonsai enhancements. If specific to analysis we may be able to argue for "new" if helpful, while still making reference to Bonsai installed base.

- *Objectives for the proposal should be detailed including individual measurable targets against which the outcome of the work will be assessed. This should refer to the objectives set out in the Je-S proposal form.*
- *Significant technical details for the development, maintenance or enhancement of the resource must be clearly outlined and indicated how this is of internationally exceptional quality.*
- *If applicable, outline any proposed research efforts and how they directly facilitate development of the resource.*
- *For proposals looking to focus on maintaining status quo for an existing resource instead of suggesting further development, you should detail evidence of why significant upgrades are not required at this time and detail why the resource needs continued support to maintain world-leading functionality.*

Additional questions that may be considered:

- *Does the facility begin or continue to support a growing field of bioscience, what is the anticipated growth and does the proposal adequately accommodate this?*
- *How will the resource accelerate science within its field and beyond?*
- *What would be the impact on the scientific community if the resource did not exist? How would this impact other, possibly dependent resources?*

1.2.1 Video-based behavioral analysis

Precisely quantifying animal behavior is an essential step toward understanding brain function. Deeplabcut is a Python-based software for tracking animal body parts (Mathis et al., 2018), which it is currently well integrated with Bonsai (Kane et al., 2020). Here we propose extensions to Bonsai to extract other informative features from video recordings.

Motion sequencing (MoSeq; Wiltschko et al., 2015): extracts patterns of behavior that repeat over time (i.e., syllables of behavior) from video data. For instance, it parses (in an unsupervised way) the behavior of a mouse in an arena into segments of time where a mouse was running, rearing and grooming. It uses a hidden Markov model and it is implemented in Python[3]. After trained MoSeq can be used to detect behavioral syllables online.

Decoding behavior from neural activity (BehaveNet; Batty et al., 2019) combines hidden Markov models with convolutional autoencoders and discriminative models to decode video data from neural recordings. It is implemented

[3]Code for MoSeq can be requested from the Datta laboratory, as indicated at http://datta.hms.harvard.edu/research/behavioral-analysis/.

in Python[4]. After trained it can be used online to decode video data and detect behavioral syllables.

Interpretable latents for behavioral videos (Partitioned Subspace Variational Autoencoder, PS-VAE; Whiteway et al., 2021): produces interpretable low-dimensional representations of behavioral videos by combining the output of pose-estimation algorithms (e.g., DeepLabCut) with unsupervised dimensionality reduction methods. These low-dimensional representations facilitate downstream behavioral and neural analyses. It is based on autoencoders and is implemented in Python[5]. After trained it can be used online to extract low-dimensional features and perform downstream processing.

1.2.2 Spike sorting

TODO

1.2.3 Low-dimensional representations of spiking data

Bonsai is well integrated with OpenEphys (Siegle et al., 2017), which allows scientists to record neural data from a large number of devices. However, it lacks functionality to process these recordings. Here we describe software that we propose to integrate into Bonsai to extract interpretable summary statistics (i.e., latent variables) from neural spiking activity.

Gaussian Linear Dynamical System (GLDS; Anderson and Moore, 2012): with sufficiently large bin sizes, spike counts can be modeled as Gaussian random processes. This Gaussianity assumption greatly simplifies the estimation of parameters of linear dynamical system (LDS) models, as well as inferences about their states. After models parameters have been learned, GLDS can be used online. A unique feature of GLDS is that the posterior distribution of states given all observation up to the present can be calculated efficiently. This estimate of the posterior distribution can be used online for experimental control, as we propose in Section 1.2.6. We will use an R implementation of GLDS which allows the use of external inputs[6].

Poisson Linear Dynamical System (PLDS; Macke et al., 2015): for smaller bin sizes, spike counts are better modeled as Poisson random processes, rather than Gaussian ones. The algorithm described in Macke et al. (2015) can estimate the parameters of a LDS, and make inferences about its states, from Poisson distributed observations. We propose to interface Bonsai with a Matlab implementation of PLDS[7] that uses variational inference. PLDS does not provide online estimates of the states, since data from a full trial is needed for state inference.

Hidden Markov Model (HMM; Rabiner, 1989): as LDSs, HMMs model a time series of observations as random processes conditioned on hidden states. However, in HMMs hidden states are discrete random variables, while in LDSs they are continuous ones. In some application domains (e.g., speech, epilepsy) discrete state assumptions are more pertinent than continuous ones. We propose to use an R implementation of HMMs[8]. As GLDSs, once trained, HMMs can be used online to infer the posterior distribution of states given observations.

Gaussian Processes Factor Analysis (GPFA; Yu et al., 2009): as LDSs, GFPA models represent a time series of observation as random processes conditioned on hidden states. However, in GPFA models the state dynamics are nonlinear, while in LDS models they are linear. Thus, GPFA models are more general than LDS ones. As GLDS models, GPFA models assume that observations conditioned on states are Gaussian random processes. We propose to use a Matlab implementation of GPFA[9]. GPFA models do not provide online estimates of the states, since data from the full trial are needed for state estimates.

Sparse Variational Gaussian Processes Factor Analysis (svGPFA; Duncker and Sahani, 2018): is similar to GPFA, but models point process observations (i.e., single spikes as opposed to spike counts). We propose to use a Python implementation of svGPFA[10]. svGPFA models do not provide online estimates of states, since data from the full trial are needed for state estimates.

Latent factor analysis through dynamical systems (LFADS; Pandarinath et al., 2018): uses an autoencoder framework, with recursive neural networks, to infer continuous states conditioned on spike counts, similar to those inferred by GPFA. We propose to use a Python implementation at LFADS[11]. As GPFA, LFADS do not provide online estimates of states.

[4] https://github.com/themattinthehatt/behavenet

[5] code for PS-VAE is embedded in the BehaveNet code https://github.com/themattinthehatt/behavenet. Please refer to class `PSVAE` in `behavenet.models.vaes.py`.

[6] https://github.com/joacorapela/kalmanFilter

[7] https://bitbucket.org/mackelab/pop_spike_dyn/src/master/

[8] https://github.com/joacorapela/hiddenMarkovModels

[9] https://users.ece.cmu.edu/ byronyu/software/gpfa0203.tgz

[10] https://github.com/joacorapela/svGPFA

[11] https://github.com/tensorflow/models/tree/master/research/lfads.

1.2.4 Low-dimensional representations of local-field potentials

Spikes are extracted from a higher-frequency range of extracellulary recorded voltages. Local field potentials (LFPs) are computed from a lower-frequency range and are another important signal to understand brain function. We propose to use states inferred from LFPs by GLDS, GPFA, HMM and LFADS (Section 1.2.3) as low-dimensional representations of the LFP.

1.2.5 Neural decoding

In order to use low-dimensional representations of spiking activity and/or of LFPs to guide the control of experiments, we need a decoder to optimally map these low-dimensional representations to experimental controls. We propose to implement in Bonsai several decoding/classification algorithms: k-nearest neighbor, linear discriminative analysis, support vector machines, random forests, artificial neural networks, naive Bayes and Gaussian process classifiers.

1.2.6 Comparing multiple data-analysis methods

We propose to add functionality to Bonsai to facilitate multi-method comparisons in user-supplied datasets. Below we describe a comparison that we will perform in Bonsai to asses the relative performance of the methods described in the previous sections with neural recordings from behaving rats. These recordings are currently being performed, to address scientific questions, at the laboratory of Prof. Akrami in the SWC. Details of the experimental task appear in Akrami et al. (2018). Briefly, in this task there are three nose ports (left, center, right). Rats initiate a trial by inserting their nose in the center port for the duration of the fixation period, until they hear a Go stimulus. During the fixation period two stimuli s_a and s_b are presented. Rats should decide which stimuli is louder. If s_a is louder than s_b the correct action is to poke the nose into the right port in order to collect a liquid reward, and if s_b is louder than s_a the correct choice is the left port.

We will use high-density Neuropixel spike and LFP recordings from the rats performing this task to learn low-dimensional representations of spiking activity and LFPs during the decision time period (between the presentation of the last auditory stimuli and the presentation of the Go stimulus), using the methods described in Sections 1.2.3 and 1.2.4. We will also learn the parameters of the classifiers described in Section 1.2.5 to optimally classify animal decisions (poke the nose into the right/left port) based on the previous low-dimensional representations.

We will compare the decoding accuracy of all decoders. This comparison will tells us, for the auditory working memory task, which neural data type (spikes or LFPs), which low-dimensional representation method (e.g., LDS or Gaussian processes), and which decoder (e.g., Bayesian or ANN) yields the best decodings in state-of-the-art neural recordings from behaving animals.

1.2.7 Interfacing Bonsai with Python, R and Matlab data analysis software

Bonsai is written in C# and most neural data-analysis methods are written in Python, R or Matlab. Fortunately, there exist software that allow C# program to call and be called by programs in these other languages. For the communication of C# programs with Python we will use Python.NET[12], with R programs we will use R.Net[13] and with Matlab we will use the built in Matlab .NET interface[14]. In cases where these software cannot support some type of communication between C# and another language we will use the messaging library ZeroMQ[15].

1.2.8 Reproducibility with Bonsai

The current version of Bonsai facilitates reproducibility of data acquisition and experimental control across laboratories. Most data acquisition and experimental control aspects of an experiment can be reproduced across different laboratories by sharing a Bonsai configuration file. By adding data analysis functionality to Bonsai, besides reproducing my data acquisition and experimental control, Bonsai users will also be able to reproduce data analysis functionality.

We will demonstrate each machine intelligence functionality added to Bonsai (Section **??**) and the multiple data-analysis methods comparisons (Section 1.2.6) in Bonsai experiments. We will then distribute Bonsai configuration files for users to reproduce these demonstrations.

1.2.9 Final remarks

We proposed to add machine intelligence functionality to Bonsai to assist users in building close-loop neural experiments: online spike sorting, methods for low-dimensional representation of spiking activity and LFPs, and neural decoding algorithms. This functionality will allow neuroscience Bonsai users to build more sophisticated experiments and extract more information from their experimental recordings.

[12] https://github.com/pythonnet/pythonnet
[13] https://github.com/rdotnet/rdotnet
[14] https://uk.mathworks.com/help/matlab/matlab_external/using-net-from-matlab-an-overview.html
[15] https://zeromq.org/

We also proposed to add functionality to help Bonsai users compare the performance of multiple methods on their datasets. With this functionality Bonsai users will be able to select the best methods to model their own recordings. It will also motivate methods developers to interface their data-analysis functionality with Bonsai. By doing so, they will provide their software to the large community of Bonsai users, and will be able to easily compare the performance of their methods with that of preexisting methods in the Bonsai ecosystem. In this way method developers will become a new type of Bonsai users, which will guarantee the sustainability of developments proposed here.

We focused this proposal on neuroscience applications of Bonsai. However, the addition of machine intelligence functionality is needed in many other experimental areas where Bonsai is or could be used. Therefore, the software abstractions that we will build to add to Bonsai machine intelligence functionality for neuroscience experiments (e.g., methods to perform multi-method comparisons) will translate to other application domains of Bonsai.

Multiple groups at the SWC currently use Bonsai for data acquisition and experimental control. Carefully testing the functionality of new software is essential to ensure its correct functionality. We propose to use the SWC large internal Bonsai user base to test the functionality we will add to Bonsai, before distributing it to the general public.

1.3 Community Demand

Evidence of community demand should be primarily driven from UK academic researchers working largely within BBSRC remit – see our Forward look for UK Bioscience for more detail on research areas covered by BBSRC. Demand from other users (such as academic communities outside of BBSRC remit or industrial users) may be appropriate to provide additional support, especially in highlighting the potential for economic, commercial or societal impact, but should not be the focus of the demand demonstration. Evidence provided should highlight examples of the high-quality science that the resource will underpin or has underpinned. Where possible and relevant, examples should be drawn from a wide research community to illustrate the broad impact of the resource to support high-quality internationally excellent science.

The level of community demand should be benchmarked against other relevant resources and/or the size of the community. This will allow the fair assessment of resources with different user bases. The types of evidence that may be appropriate to provide will be different for new and existing resources.

Evidence of wider consultation of the prospective community (e.g community surveys) is encouraged.

New Resources

New resources should estimate the number of researchers who may engage and benefit from the resource. Evidence, where possible, would be of benefit and may include:

- *Datasets (or samples) in public or private repositories*
- *Citations or acknowledgments*
- *Gap analysis with existing resources*
- *Pilot project uptake or feedback from potential users.*

In particular, proposals for new resources should have consulted their prospective community prior to application

Existing Resources

For existing resources this should include usage data of the current resource. Data types may include:

- *Access requests from independent users/ sites*
- *Citations or acknowledgements*
- *Other public resources providing links to the resource*
- *New major acquisitions captured by the resource*

Additionally, existing resources need to evidence why this resource needs to be maintained/updated by the current grant. This could include:

- *Survey data from users on what upgrades are needed*
- *Evidence of an expanding user base, which requires additional resource*
- *Recent developments in the field, which require upgrades to be integrated into the resource.*

1.4 User engagement

Discussion of user engagement provision should aim to answer the following questions:

- *Is there awareness of the resource within the user community?*
- *How do you plan to develop the engagement strategy within the proposal timeframe to expand user engagement?*
- *How have access mechanisms to ensure usability of the resource been considered?*
- *How have user needs been incorporated into this proposal to ensure it is fit for purpose and will deliver on expectations?*

New Resources

Evidence should be provided as to how the resource plans to engage stakeholders and ensure that the resource meets their needs and is used by the community targeted by the resource.

Existing Resources

Evidence should be provided as to whether the resource has achieved the level of engagement it originally anticipated, and consideration is given how the additional investment would change this.

1.5 Long term sustainability planning

In addition, the case for support should outline considerations for the long- term sustainability of the resource beyond UKRI-BBSRC funding, as well as the true cost of running and maintaining the resource in question. The proposal should include:

- *Cost recovery plans, where appropriate, or an explanation why not if not viable. Evidence of clear business planning with a focus on at least partial cost recovery is required, especially when applying as an existing resource.*
- *Details for alternative support plans, aside from UKRI-BBSRC funding.*
- *The level of support the resource is projected to require for expected maintenance and/or subsequent maturation/enhancement activities. Clear arguments as to why UKRI-BBSRC should support the resource now should be provided, if other cost recovery and support plans are deemed unsuitable.*

1.6 Potential for economic and societal impact

Outline how the outputs of the proposed resource will contribute to knowledge and how this may have the potential for economic return or societal benefits. Impact activities should be integrated into appropriate sections of the case for support, not presented as an independent work package.

- *All proposals are expected to demonstrate clear plans with recorded milestones and timelines for associated activities to develop economic, commercial and societal impacts. August 2021 7*
- *Methods of engagement and measures of success should be outlined including how these will be regularly reviewed throughout the project in order to deliver the most impact.*
- *Any planned activities should be fully justified within the Justification of Resources attachment*

1.7 Track Record

The majority of the track record relevant to the project should be located within the Narrative CV and should not be repeated within the case for support. You may, however, want to describe:

- *Track record of the team working together*
- *Specific expertise available at the host organisation and any proposed partner organisations to enable the successful delivery of the project.*
- *The specific role of each applicant and collaborator in the project*

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